REMARKS

In the Office Action dated June 23, 2004, claims 1-31 were examined with the result that all claims were rejected. In response, Applicant submits the following remarks. In view of these remarks, reconsideration of this application is requested.

In the Office Action, the Examiner rejected claims 1-31 as filed based upon double patenting of the "same invention" type as well as of the "obvious" type in view of two copending patent applications and two issued U.S. patents. These rejections can be found in paragraphs 1-6 of the Office Action. In paragraphs 7 and 8 of the Office Action, the Examiner rejected claims 1-31 under 35 USC §103(a) based upon four U.S. patents. Applicant would like to first discuss the §103 claim rejections and then return to the double patenting rejections later in these comments.

35 USC §103 Claim Rejections

In the Office Action, claims 1-31 were rejected under 35 USC §103(a) as being unpatentable over DeLuca et al U.S. Patent Nos. 5,843,928; 6,114,317; 6,392,071 and 6,696,431. The Examiner states that each of these references teach 2-alkylidene-19-nor-vitamin D compounds and although claims 1-31 of the present application differ from the above-cited references by reciting a compound not exemplified by these prior art references, it would have been obvious to one of ordinary skill in the art to select any of the species of the genus taught by these references, including the presently claimed compound, because it would have been reasonable to expect any of the species of the genus to have similar properties and thus have similar uses. Applicant, however, respectfully disagrees for the following reasons.

The present invention is directed toward 2-methylene-19-nor-20(S)-25-methyl-1α-hydroxycalciferol (hereinafter referred to as TMM) and various uses for this compound, namely, treating metabolic bone disease (claims 6-17), treating psoriasis (claims 18-20), and treating a cancerous disease (claims 21-30). The uses claimed are

based upon the biological activity of TMM reported in the specification. In this regard, Applicant refers the Examiner to page 18 of the specification as filed wherein the data presented in the specification and drawings is described and summarized. More specifically, TMM was found to have significant cell differentiation activity and this cell differentiation activity is essentially equal to that of 1α,25-dihydroxyvitamin D_3 (the native hormone against which all vitamin D compounds are typically compared). The fact that TMM has relatively high differentiation activity indicates that TMM may have significant activity against psoriasis. The activity of TMM in causing cellular differentiation and suppression of HL-60 cell growth is also consistent with a potential use in the treatment of malignant disease. With respect to calcemic activity, TMM was determined to have very little bone calcium mobilization activity, i.e. significantly less potent than 1α,25-dihydroxyvitamin D_3 in such activity, and it was also determined that TMM had a very strong effect on intestinal calcium absorption, i.e. about 10 times greater than that of 1α,25-dihydroxyvitamin D_3. Thus, TMM shows selectivity for activity on intestinal calcium absorption, but not bone calcium mobilization. As stated on page 18 of the specification, TMM could thus be used as a maintenance vitamin D compound in patients where high gut calcium absorption is needed but where bone calcium mobilization is not desired, and specifically mentions osteoporosis. In summary, TMM has significant cell differentiation activity, and has high intestinal calcium transport activity, but has very little bone calcium mobilization activity, as compared to 1α,25-dihydroxyvitamin D_3.

Referring now to the references cited by the Examiner, U.S. 5,843,928 teaches that the 2-alkylidene compounds disclosed therein are characterized by (1) high cell differentiation activity, (2) little, if any, intestinal calcium transport activity and (3) relatively high bone calcium mobilization activity, as compared to 1α,25-

dihydroxyvitamin D_3. Applicant refers the Examiner to column 4, lines 5-13 as well as column 4, lines 43-47. Thus, as the Examiner can see, the biological activities disclosed in the '928 patent are significantly different from the biological activities disclosed in the present patent application. In fact, the '928 patent discloses calcemic activity for the compounds described therein which appears to be exactly the opposite from that described in the present patent application. In the '928 patent, compounds have little, if any, intestinal calcium transport activity and high bone calcium mobilization activity. In contrast, the compound of the present invention has high intestinal calcium transport activity, but little, if any, bone calcium mobilization activity. Thus, as stated by the Examiner, one would expect their activities to be similar in view of their structural similarity. As noted above, however, these activities are not similar resulting in TMM not being obvious in view of the '928 patent. Thus, Applicant requests the Examiner withdraw the rejection based on the '928 reference.

With regard to U.S. 6,392,071 and U.S. 6,696,431, these two patents are related as emanating from the same parent application, i.e. U.S. 5,843,928, and essentially disclose and claim the same four compounds (the '071 patent) as well as their use in treating psoriasis (the '431 patent). Applicant refers the Examiner to the bottom of column 4 in each patent as well as the second full paragraph in column 5 of each patent for a description of the biological activities of the four compounds described and claimed in these two references. More specifically, it is stated that these four compounds are characterized by relatively high intestinal calcium transport activity, while also exhibiting relatively high bone calcium mobilization activity, as compared to 1α,25-dihydroxyvitamin D_3. In other words, both intestinal calcium transport activity and bone calcium mobilization activity are greater than 1α,25-dihydroxyvitamin D_3. In contrast, TMM shows biological activity different from the four compounds disclosed in the '071 and '431 references. More specifically, TMM

has high intestinal calcium absorption activity, but very little bone calcium mobilization activity. Thus, once again, as stated by the Examiner, one would expect their activities to be similar since they are similar in structure. However, as noted above, these activities are not similar resulting in TMM not being obvious in view of the compounds disclosed in the '071 and '431 references. Accordingly, Applicant requests the Examiner withdraw the §103 rejection based on the '071 and '431.

With regard to U.S. 6,114,317, this patent is directed toward a method of modifying or altering the structure of a 1α-hydroxylated vitamin D compound to increase its biological activity by altering the conformational equilibrium of the A-ring to favor a chair conformation that presents the 1α-hydroxyl in its axial orientation. This is accomplished by either locking the A-ring chair conformation in a geometry having an axially orientated 1α-hydroxyl, or by the addition of one or more substituents to the A-ring which interact with other substituents in the molecule or on the A-ring to provide a driving force to the A-ring to adopt a chair conformation which presents the 1α-hydroxyl in its axial orientation. Applicant refers the Examiner to column 1, lines 15-23 wherein it is stated that as a result of presenting the 1α-hydroxyl in its axial orientation, vitamin D compounds can be synthesized having greater biological activity, as compared to 1α,25-dihydroxyvitamin D_3 in one or more of its calcemic activities, i.e. intestinal calcium transport activity, bone mineralization activity and bone calcium mobilization activity, or in cell differentiation activity. However, the Examiner should note that the '317 patent does not present any biological data on the calcemic activities of any of the compounds disclosed and/or claimed therein. The '317 reference does not disclose any biological activity for the compounds taught therein except that those compounds would have greater biological activity than 1α,25-dihydroxyvitamin D_3 in one more of its calcemic activities and/or cell differentiation activity. In contrast, the present specification specifically states

that TMM has high intestinal calcium transport activity, but very little bone calcium mobilization activity. In addition, the Examiner should note the scope of the structure set forth in columns 5 and 6 of the '317 patent. The structural formula covers a multitude of vitamin D compounds, and there is no reason set forth in the '317 reference which would cause one skilled in the art to select only TMM from the huge number of compounds covered by the structural formula since there is nothing in the '317 reference which would direct one skilled in the art to select TMM. Thus there is no real motivation set forth in the '317 reference which would cause one skilled in the art to select TMM out of the huge number of compounds covered by the structural formula since one skilled in the art must choose between eight variables on the A-ring and eight variables on the side chain in order to arrive at TMM. Thus, except for the fact that TMM is broadly covered by the generic formula in the '317 patent, there is nothing in the '317 patent which would motivate one skilled in the art to select TMM from the huge number of compounds covered by the generic formula. Thus, Applicant requests the Examiner withdraw the §103 rejection based on the '317 patent.

The Double Patenting Claim Rejections

In paragraph 2 of the Office Action, claims 1-31 were rejected under 35 USC §101 as claiming the same invention as that of claims 1-31 of copending application No. 10/613,201. In response, Applicant advises the Examiner that Applicant has filed an express abandonment of Application No. 10/613,201. The express abandonment was faxed to the Pre-Grant Publication Division of the U.S. PTO on September 15, 2004. That application was, unfortunately, filed in error and thus was expressly abandoned by Applicant.

In paragraph 5 of the Office Action, claims 1-20 were rejected under the Doctrine of Obviousness Type Double Patenting as being unpatentable over numerous

claims of U.S. 5,843,928. In response, Applicant refers the Examiner to the remarks set forth previously herein with regard to the '928 reference. In accordance therewith, Applicant believes that the biological activities disclosed in the '928 patent are significantly different from the biological activities disclosed in the present patent application with regard to TMM. The compounds in the '928 reference have high bone calcium mobilization activity and little, if any, intestinal calcium transport activity, whereas TMM has very little bone calcium mobilization activity, but high intestinal calcium absorption activity. These activities of TMM are directly opposite from what is stated as being the biological activities of the compounds in the '928 patent. Thus, these activities are directly opposite from what would be expected due to the structural similarity between TMM and the compounds of the '928 patent. In view of these different activities, Applicant believes the Examiner should withdraw the obviousness type double patenting rejection based on the '928 patent.

In paragraph 6 of the Office Action, claims 1-17 were rejected under the Doctrine of Obviousness Type Double Patenting as being unpatentable over several claims of U.S. 6,114,317. Applicant, however, once again refers the Examiner to the remarks previously made herein with respect to the '317 patent. Since there is no biological activity disclosed in the '317 patent for the compounds covered by the generic formula therein, but there is merely a general statement that one or more calcemic activity is increased by the method disclosed therein, Applicant believes there is no motivation to one skilled in the art to select TMM from the huge number of compounds covered by the generic formula in the '317 patent. As previously noted herein, one skilled in the art must select between eight different variables on the A-ring and eight different variables on the side chain in order to arrive at TMM. There is clearly no teaching in the '317 patent which would direct one skilled in the art to make

all of the appropriate selections for these variables in order to arrive at TMM. As a result, Applicant believes the Examiner should withdraw the obviousness type double patenting rejection based on the '317 patent.

Finally, Applicant refers the Examiner to paragraph 4 of the Office Action where claims 3-5 and 18-30 were rejected under the Doctrine of Obviousness Type Double Patenting as being unpatentable over numerous claims of copending Application No. 10/235,244. Application No. 10/235,244 is directed toward a method of administering a toxic dose of a vitamin D compound without developing hypercalcemia by administering a bone calcium resorption inhibitor either before or simultaneously with a vitamin D compound. The claims referred to by the Examiner in the rejection are directed toward methods of treating psoriasis, cancerous diseases, and pharmaceutical compositions containing the bone calcium inhibitor and/or the vitamin D compound. Once again, it is important to note that although the generic formula set forth in the copending application covers TMM, one skilled in the art must select between five variables on the A-ring and eight variables on the side chain in order to arrive at TMM. There is no express teaching in the copending application of a particular reason to select TMM from all of the compounds covered by the genus. It just happens that TMM is one of the compounds covered by the structural formula of the genus in the copending application. There are no "preferred" species or subgenus referred to in the copending application, and although there are teachings of similar properties or uses, there is nothing in the copending application which would provide any particular reason to select TMM from all of the compounds covered by the genus. The copending application is directed toward methods of controlling the toxicity of vitamin D compounds and thus no specific teaching would lead one skilled in the art to select TMM from the genus disclosed therein.

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,

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